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Trends in Antifungal Use and Epidemiology of Nosocomial Yeast Infections in a University Hospital

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This report describes both the trends in antifungal use and the epidemiology of nosocomial yeast infections at the University of Iowa Hospitals and Clinics between fiscal year (FY) 1987–1988 and FY 1993–1994. Data were gathered retrospectively from patients' medical records and from computerized databases maintained by the Pharmacy, the Program of Hospital Epidemiology, and the Medical Records Department. After fluconazole was introduced, use of ketoconazole decreased dramatically but adjusted use of amphotericin B decreased only moderately. However, the proportion of patients receiving antifungal therapy who were treated with amphotericin B declined markedly. In FY 1993–1994, 26 patients of the gastrointestinal surgery service received fluconazole. Among these patients, fluconazole use was prophylactic in 16 (61%), empiric in 3 (12%), and directed to a documented fungal infection in 7 (27%). Rates of nosocomial yeast infection in the adult bone marrow transplant unit increased from 6.77/1,000 patient days in FY 1987–1988 to 10.18 in FY 1989–1990 and then decreased to 0 in FY 1992–1993. Rates of yeast infections increased threefold in the medical and surgical intensive care units, reaching rates in FY 1993–1994 of 6.95 and 5.25/1,000 patient days, respectively. The rate of bloodstream infections increased from 0.044/1,000 patient days to 0.098, and the incidence of catheter-related urinary tract infections increased from 0.23/1,000 patient days to 0.68. Although the proportion of infections caused by yeast species other than *Candida albicans* did not increase consistently, *C. glabrata* became an important nosocomial pathogen.

Since the early 1980s, the frequency of nosocomial yeast infections has increased dramatically. Data from the National Nosocomial Infections Surveillance System indicate that between 1980 and 1989, the incidence of nosocomial candidemia increased by about 500% in large teaching hospitals (3). *Candida* spp. currently are the fourth most common nosocomial pathogens in intensive care units (18). Several investigators have reported that the incidence of infections caused by species other than *Candida albicans* has increased (1, 22, 24, 28). However, other investigators have reported that *C. albicans* is still the most common *Candida* species causing nosocomial infections (23, 36).

In 1990, the use of fluconazole, a new antifungal agent, was introduced in the United States. This triazole compound is less toxic than amphotericin B, has excellent bioavailability after oral administration, can be administered intravenously, and has broad-spectrum activity against yeast (30). Consequently, physicians began using fluconazole for various clinical indications, although supporting data from controlled trials were not yet available (16).

Fungal isolates obtained from patients can be resistant to fluconazole. Particular yeast species, such as *Candida krusei*, are intrinsically resistant to fluconazole, and isolates of *Candida glabrata* and *C. albicans* that are initially susceptible may become resistant during treatment. Investigators have not determined whether short courses of fluconazole will select resistant isolates (29), but some investigators have predicted that indiscriminate use of fluconazole will select resistant strains and species (1, 7, 28, 29).

The objective of the present study was to describe both the trends in antifungal use and the epidemiology of nosocomial yeast infections at the University of Iowa Hospitals and Clinics (UIHC) between fiscal year (FY) 1987–1988 and FY 1993–1994. In addition, we evaluated in greater detail the epidemiology of fluconazole use during FY 1993–1994.

MATERIALS AND METHODS

Antifungal use. The UIHC is a 900-bed tertiary-care center. The Pharmacy Department maintains a continuous, computerized record of the antimicrobial agents dispensed. The total numbers of grams and doses of amphotericin B, fluconazole, ketoconazole, and itraconazole used by each nursing unit between FY 1987–1988 and FY 1993–1994 were obtained from this database.

The patients who were treated with fluconazole during FY 1993–1994 were identified from the Pharmacy Department's database. Each patient's medical record abstract was reviewed to identify the patient's medical diagnoses and to determine which operative procedures the patient underwent during the specified admission. In addition, the medical records of all patients who received fluconazole and who underwent gastrointestinal surgery during FY 1993–1994 were reviewed to identify the indications for which fluconazole was given. Three categories of fluconazole use were defined. Use was defined as prophylactic if fluconazole was given perioperatively to a patient who had no evidence of fungal infection or whose physician stated in the progress notes that the drug was given prophylactically. Use was defined as empirical if (i) fluconazole was administered to a patient who did not have fungi isolated from cultures but had signs of infection (e.g., fever, leukocytosis, local inflammation) despite antibiotic therapy or (ii) the patient's physician stated in the progress notes that fluconazole was used to treat a presumed fungal infection. Use was defined as specific if fluconazole was prescribed for a patient who had a fungus isolated from at least one culture at any site. If patients received more than one course of fluconazole, the first course was evaluated.

Nosocomial yeast infections. Since 1976, the Program of Hospital Epidemiology has conducted hospital-wide concurrent surveillance for bacterial and fungal nosocomial infections. The definitions of infection were adapted from the original definitions published by the Centers for Disease Control (32). The surveillance system was prospectively validated in 1987 (8). Data on nosocomial yeast infections were obtained from the Program's database.

For the current study, a nosocomial yeast infection was defined as any infection that occurred more than 48 h after the patient was admitted to the hospital

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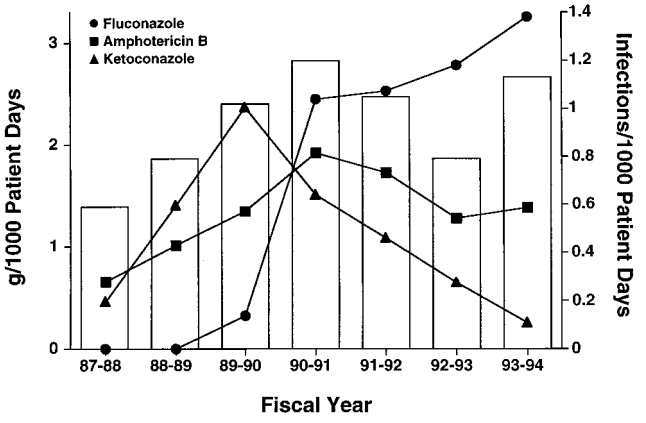

FIG. 1. Adjusted rates of antifungal use and adjusted rates of nosocomial yeast infections during each FY of the study period.

from which at least one species of yeast was isolated. We excluded results of cultures from the skin, vagina, mouth, esophagus, and upper and lower respiratory tracts.

Cultures and microbiologic methods. Cultures were collected at the discretion of the clinical staff and processed by standard microbiologic methods. Fungal isolates were identified to the species level by using the Vitek YBC System (bioMerieux Vitek, St. Louis, Mo.) and conventional methods as needed. All fungal isolates from cultures of blood and normally sterile body sites were identified to the species level. Fungal isolates from other sites usually were characterized as *Candida* species based upon microscopic appearance, colony morphology, and the germ tube test. Fungal isolates from other sites were identified to the species level, when indicated clinically, by using the Vitek YBC System.

RESULTS

Antifungal use. The number of grams of each antifungal agent used each year (crude use) varied substantially during the study period. Crude use of ketoconazole increased from 106 g in FY 1987–1988 to 490 g in FY 1989–1990 but then decreased to 41 g by FY 1993–1994. Crude use of amphotericin B increased from 151 g in FY 1987–1988 to 349 g in FY 1991–1992 and then decreased to 225 g in FY 1993–1994. Crude use of fluconazole increased rapidly after April 1990, when the drug was introduced. By FY 1991–1992, the second year after its release, 511 g of fluconazole was used. Thereafter, the number of grams used increased gradually to 529 g in FY 1993–1994. Crude use of itraconazole, which was introduced in FY 1992–1993, reached 202 g by FY 1993–1994.

The adjusted rate of ketoconazole use (the number of grams used per 1,000 patient days) increased from FY 1987–1988 through FY 1989–1990 but then decreased dramatically (Fig. 1). The adjusted rate of amphotericin B use increased threefold between FY 1987–1988 and FY 1990–1991, decreased between FY 1990–1991 and FY 1992–1993, and then remained stable through FY 1993–1994. In contrast, the adjusted rate of fluconazole use increased each year during the study period, with the most substantial increase occurring in FY 1990–1991.

The adjusted rates of antifungal use were compared among several units (Fig. 2A to F). The adult bone marrow transplant unit (BMTU) was the first to begin using fluconazole (Fig. 2A). Fluconazole use was highest in FY 1990–1991, when 45 g was used per 1,000 patient days. Subsequently, fluconazole use by the BMTU decreased to 21 g/1,000 patient days in FY 1993–1994. During the same time period, amphotericin B use gradually decreased from 36 to 25 g/1,000 patient days, whereas ketoconazole use peaked in FY 1989–1990 and then decreased each year thereafter. The adult hematology unit (Fig. 2B) and the medical intensive care unit (MICU) (Fig. 2C) began using fluconazole later than the adult BMTU. Fluconazole use in the adult hematology unit and in the MICU fluctuated during the study period, but increased use of fluconazole was not associated with substantially decreased use of amphotericin B (Fig. 2B and C).

The surgical intensive care unit (SICU) began using fluconazole in FY 1990–1991, and use increased steadily to 7.5 g/1,000 patient days in FY 1992–1993 (Fig. 2D). Subsequently, fluconazole use decreased slightly. During the study period, use of amphotericin B changed very little and ketoconazole use was negligible. The solid-organ transplant unit also began using fluconazole in FY 1990–1991 (Fig. 2E). The rate of use increased most dramatically during the first year and then increased gradually from 4.6 g/1,000 patient days in FY 1991–1992 to 6.3 g/1,000 patient days in FY 1993–1994. During this time period, however, the rate of amphotericin B use did not change substantially. The gastrointestinal surgery unit used very little fluconazole until FY 1991–1992. Subsequently, fluconazole use increased rapidly from 1.0 to 7.3 g/1,000 patient days. In contrast, this unit used very little amphotericin B either before or after fluconazole was introduced (Fig. 2F).

Crude and adjusted rates of antifungal use during FY 1993–1994 were compared among nursing units. Crude (Fig. 3A) and adjusted (Fig. 3B) use of amphotericin B was highest in the adult BMTU. This unit also used 39% of the total amount of ketoconazole prescribed during that year, followed by the genitourinary surgery (17%) and adult hematology (17%) units. In contrast, the crude use of fluconazole (Fig. 4A) was highest in the general medicine units (22%), followed by the adult BMTU (12%), the gastrointestinal surgery unit (10%), the pediatric BMTU (10%), and the SICU (8%). However, when adjusted for the number of patient days, fluconazole use was highest in the adult and pediatric BMTUs (Fig. 4B).

In FY 1993–1994, 281 patients received one or more courses of fluconazole. The primary groups of patients receiving fluconazole were those with human immunodeficiency virus infection, those undergoing nononcologic surgery, and those with solid-organ transplants (Fig. 5). Of the 44 nononcologic surgical patients who received fluconazole, 26 (59%) were patients who underwent gastrointestinal surgery. The initial reason that fluconazole was used for those patients was categorized as prophylactic in 16 (61%) patients, empiric in 3 (12%) patients, and directed to a documented fungal infection in 7 (27%) patients.

Trends in nosocomial yeast infections. Between FY 1987–1988 and FY 1993–1994, 1,268 nosocomial yeast infections were identified. The crude number of infections varied from 134 to 214/year. The rates of yeast infection increased by 186% from 0.59/1,000 patient days in FY 1987–1988 to 1.10/1,000 patient days in FY 1993–1994. The highest incidence of infection, 1.20/1,000 patient days, occurred in FY 1990–1991 (Fig. 1). The units with the highest rates of infection were the MICU, the SICU, the hematology unit, the solid-organ transplant unit, and the adult and pediatric BMTUs. The rates of nosocomial yeast infections per 1,000 patient days during FY 1993–1994 were as follows: MICU, 6.95; SICU, 5.25; adult hematology unit, 3.53; solid organ transplant unit, 2.12; adult BMTU, 1.66. Changes in the rates of nosocomial fungal infections and changes in use of antifungal agents were not clearly related (Fig. 1 and 2A to F).

The trends in infection rates varied greatly between units (Fig. 2A to F). For instance, in the hematology unit, the incidence density rate did not change substantially over the study period (Fig. 2B). However, the average time from admission to the onset of infection decreased from 19.5 to 11.6 days. In

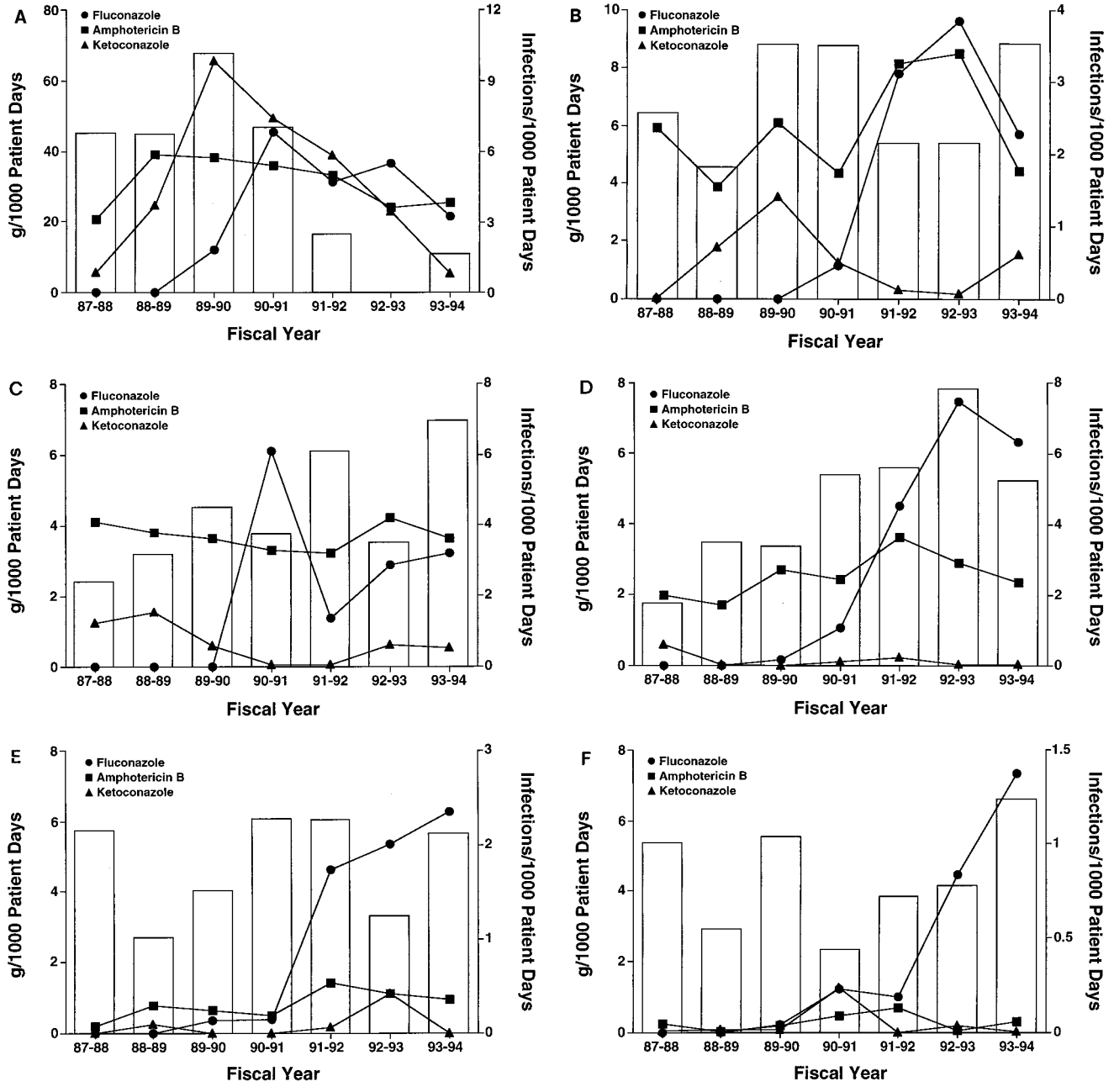

FIG. 2. Adjusted rates of antifungal use and adjusted rates of nosocomial yeast infections by unit during each year of the study period. (A) Adjusted rates of antifungal use and adjusted rates of nosocomial yeast infections in the adult BMTU. (B) Adjusted rates of antifungal use and adjusted rates of nosocomial yeast infections in the adult hematology unit. (C) Adjusted rates of antifungal use and adjusted rates of nosocomial yeast infections in the MICU. (D) Adjusted rates of antifungal use and adjusted rates of nosocomial yeast infections in the SICU. (E) Adjusted rates of antifungal use and adjusted rates of nosocomial yeast infections in the solid-organ transplant unit. (F) Adjusted rates of antifungal use and adjusted rates of nosocomial yeast infections in the gastrointestinal surgery unit.

contrast, the rate of infection in the adult BMTU increased dramatically from 6.77 infections per 1,000 patient days in FY 1987–1988 to 10.18 in FY 1989–1990, when 32 infections occurred per 100 admissions (Fig. 2A). The rates then decreased each year until FY 1992–1993, when no nosocomial yeast infections were identified. The adjusted rates of yeast infections in the two intensive care units increased threefold, reaching rates in FY 1993–1994 of 6.95/1,000 patient days in the MICU (Fig. 2C) and 5.25/1,000 patient days in the SICU (Fig. 2D).

Trends in infection sites. Infections caused by yeast were observed at eight different sites: bloodstream, eye, central nervous system, gastrointestinal tract or intraabdominal site, intravascular catheters, urinary tract, surgical site, and other wounds. However, infections of the urinary tract (36 to 68%), bloodstream (6 to 11%), surgical sites (9 to 18%), and the gastrointestinal tract or intraabdominal site (5 to 35%) accounted for at least 80% of all infections each year (Fig. 6). Ninety percent of all urinary tract infections (UTIs) were catheter related.

The annual adjusted rate of bloodstream infections increased throughout the study period from 0.044 to 0.098/1,000 patient days, and the incidence of catheter-related UTIs in-

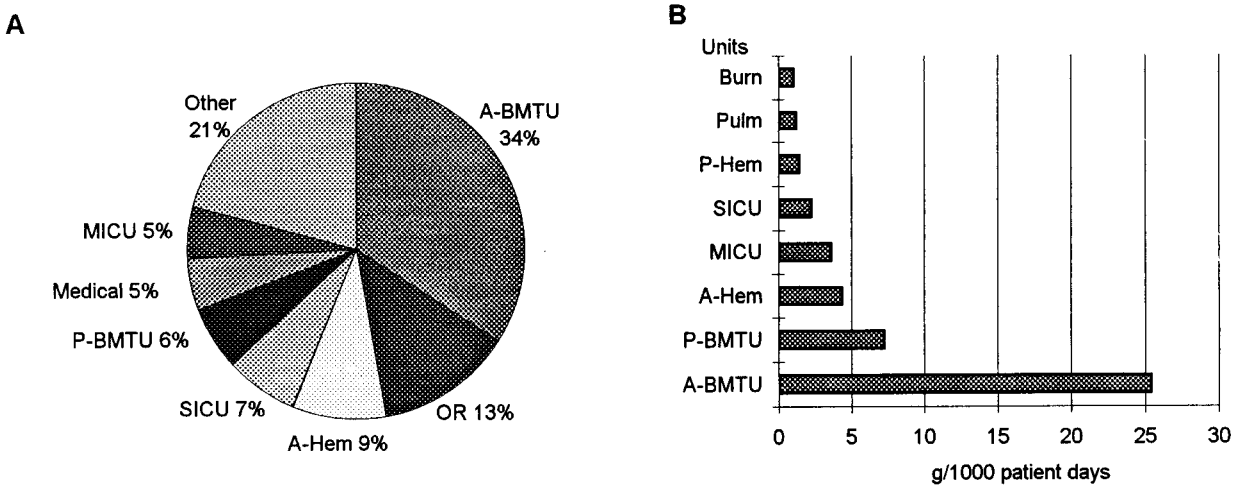

FIG. 3. Amphotericin B use in FY 1993–1994. (A) Amphotericin B use by each unit in FY 1993–1994 as a proportion of the total amount (grams) used (n = 225 g). Abbreviations: adult BMTU, A-BMTU; operating room, OR; adult hematology unit, A-Hem; pediatric BMTU, P-BMTU; general internal medicine unit, Medical; other units, Other. (B) Adjusted amphotericin use (grams per 1,000 patient days) by major units. Abbreviations: pediatric hematology unit, P-Hem; pulmonary unit, Pulm; burn unit, Burn.

creased threefold, from 0.23 to 0.68/1,000 patient days. In contrast, the annual rates of surgical site infections changed little during the study period, ranging between 0.09 and 0.14/1,000 patient days. The rate of intraabdominal and gastrointestinal infections decreased substantially during the last 3 years of the study.

The distribution of infections by site varied greatly between units. Nearly half of the fungal bloodstream infections occurred in the SICU and the hematology unit, whereas about 70% of the abdominal and gastrointestinal infections occurred in the two BMTUs and the hematology unit. One-third of the UTIs occurred in the two intensive care units. In fact, all nosocomial yeast infections in the MICU during FY 1989–1990 were catheter-related UTIs.

Trends in the yeast species that caused nosocomial infections. *C. albicans* was the most common yeast species among the isolates identified to the species level. The proportion of yeast isolates from all sites that were not identified to the species level ranged from 31 to 43%. Overall, the proportion of nosocomial yeast infections caused by *C. albicans* decreased from 49% in FY 1987–1988 to 23% in FY 1993–1994 (Fig. 7). *C. glabrata* was the only species other than *C. albicans* that caused a substantial number of the infections, and the proportion of all nosocomial yeast infections caused by *C. glabrata* increased substantially during the study period (Fig. 7). No *C. glabrata* infections were identified in FYs 1987–1988 and 1988–1989; subsequently, *C. glabrata* caused 21 to 30% of all nosocomial yeast infections (Fig. 7), including 30 to 36% of UTIs

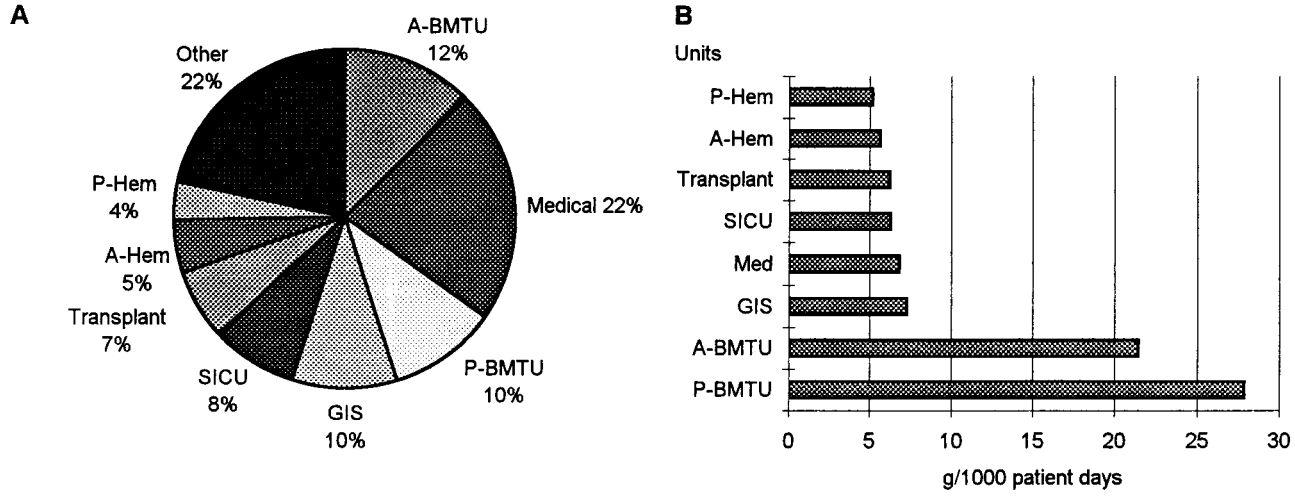

FIG. 4. Fluconazole use in FY 1993–1994. (A) Fluconazole use by each unit in FY 1993–1994 as a proportion of the total amount (grams) used (n = 529 g). (B) Adjusted fluconazole use (grams/1,000 patient days) by major units. Abbreviations: adult BMTU, A-BMTU; adult hematology unit, A-Hem; pediatric BMTU, P-BMTU; general internal medicine unit, Medical; other units, Other; pediatric hematology unit, P-Hem; solid-organ transplant unit, Transplant; gastrointestinal surgery unit, GIS.

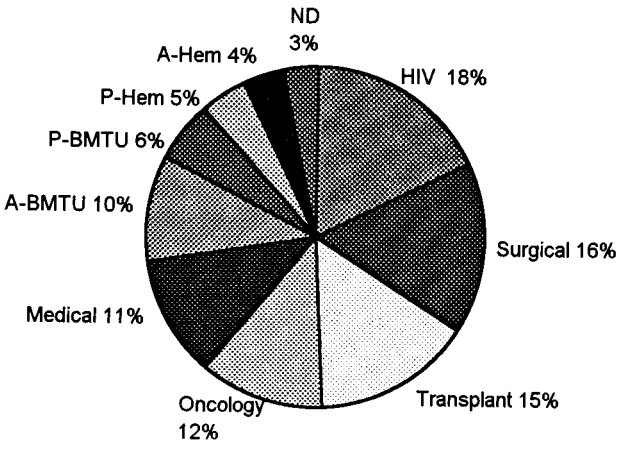

FIG. 5. Categories of patients who received fluconazole in FY 1993–1994. The total number of patients was 281. Adult BMTU patients (A-BMTU), adult patients with hematologic diseases (A-Hem), pediatric BMTU patients (P-BMTU), adult patients with general medical diseases (Medical), pediatric patients with hematologic diseases (P-Hem), patients undergoing solid-organ transplantation (Transplant), human immunodeficiency virus-infected patients (HIV), patients undergoing nononcologic operative procedures (Surgical), patients with solid-organ tumors who were undergoing medical or surgical treatment (Oncologic), and patients whose underlying conditions had not been determined (ND) were included.

and 8 to 20% of bloodstream infections. No other species accounted for more than 3% of all nosocomial yeast infections. The yeast species causing infections did not vary substantially by unit, except that 96% of the *Saccharomyces* infections occurred in either the adult hematology unit or the adult BMTU.

A variety of yeast species caused nosocomial bloodstream infections; however, *C. albicans* was the most common etiologic agent. The proportion of bloodstream infections caused by this species varied markedly by year, but no clear trend appeared during the study period. The proportion of bloodstream infections caused by *C. glabrata* increased steadily from 0% in the first 2 FYs of the study to 20% in FY 1991–1992 and then declined (data not shown). The average proportion of nosocomial bloodstream infections caused by *C. glabrata* was 8%. The proportion of bloodstream infections caused by other yeast species varied dramatically each year. On average, other yeast species caused fewer than 15% of all nosocomial bloodstream infections: *Cryptococcus neoformans*, 13%; *C. tropicalis*, 10%; *C. parapsilosis*, 9%; *C. krusei*, 5%; *Trichosporon* spp., 4%; *Candida lusitaniae*, 1%.

DISCUSSION

During the 1980s, numerous investigators reported that the frequency of severe, life-threatening infections caused by yeasts, especially *Candida* spp., increased dramatically (3, 18, 21). Many patients who acquire such yeast infections have serious underlying medical conditions. However, disseminated yeast infections increase the mortality rate above that expected for the underlying disease. For example, Wey et al. reported that candidemia has an attributable mortality of 38% (35). Because disseminated fungal infections have such high attributable mortality rates, several investigators have evaluated the prophylactic use of antifungal agents in specific patient populations (14, 27).

Fluconazole is a particularly attractive agent for prophylactic use because it is absorbed well from the gastrointestinal tract and because it is much less toxic than amphotericin B. Before fluconazole was introduced, Grasela et al. conducted a multicenter study in which they evaluated 786 patients who received antifungals (15). During this time period, amphotericin B was the drug most frequently used for documented or presumed systemic fungal infections. Ketoconazole was the drug used most often as a prophylactic agent and as treatment for oral and esophageal infections. Those investigators subsequently reported that antifungal therapy use changed dramatically 1 year after fluconazole was introduced (16). At that time, fluconazole was already the agent used most frequently for presumed or documented infection at all sites except the bloodstream.

At the UIHC, introduction of fluconazole essentially eliminated the use of ketoconazole but did not substantially decrease the crude or adjusted use of amphotericin B. However, the proportion of patients receiving antifungal therapy who were treated with amphotericin B declined markedly.

Our data indicate that fluconazole is used frequently as either empiric or prophylactic treatment for patients who are perceived to be at risk for yeast infections. For example, pa-

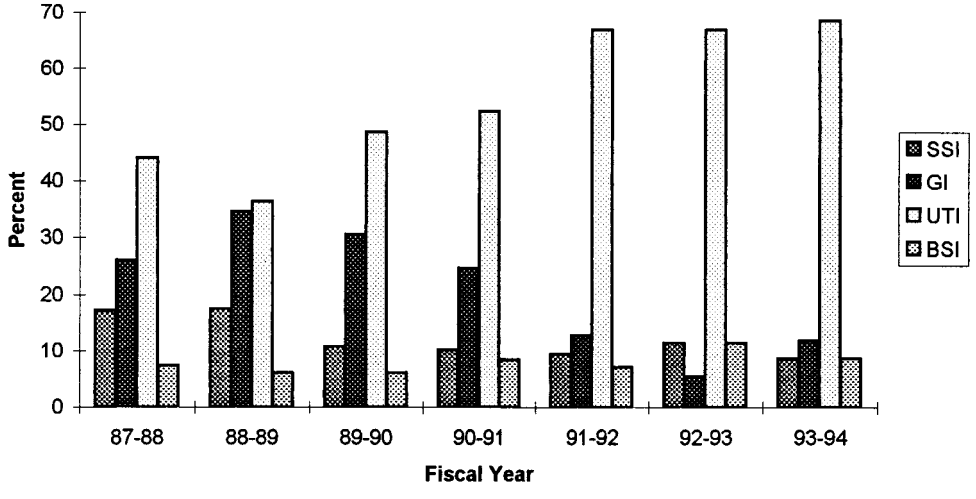

FIG. 6. Distribution of nosocomial yeast infections by site during each year of the study period. Abbreviations: bloodstream infection, BSI; gastrointestinal infection, GI; surgical site infection, SSI.

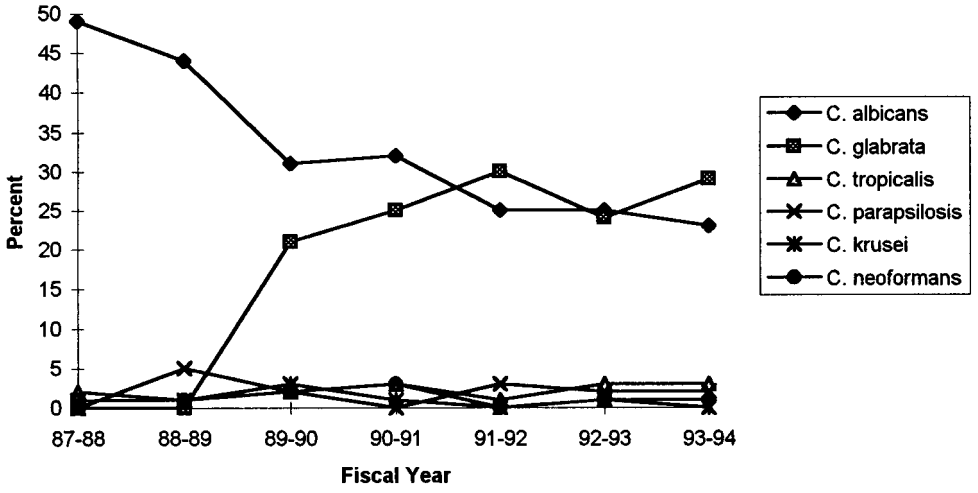

FIG. 7. Proportion of nosocomial yeast infections caused by different yeast species during each year of the study period.

tients undergoing gastrointestinal surgery were rarely treated with amphotericin B, which is very toxic. However, 73% of those patients who received fluconazole in FY 1993–1994 were treated prophylactically or empirically. In fact, our surgeons used fluconazole prophylactically for all patients undergoing kidney, liver, or pancreas transplants. Thus, surgeons apparently use fluconazole, a less toxic agent, prophylactically even though there are no data supporting this practice.

During the study period, the rates of nosocomial yeast infections varied greatly between units. For example, adjusted annual rates of yeast infections increased in the MICU and SICU during the course of the study. In contrast, the rate of yeast infections decreased dramatically after FY 1989–1990 in the adult BMTU and remained stable over the study period in the hematology unit. Other authors also have suggested that the rate of nosocomial fungal infections in oncology patients is no longer increasing (4).

The incidence of yeast bloodstream infections increased during the study period. The increased infection rates might be explained in part by transmission of a single strain within a unit (i.e., an outbreak), not by a sustained increase in the number of patients at risk for yeast infections. Indeed, outbreaks of yeast infections have been identified (12, 23–26). In addition, health care workers can carry yeast on their hands (3) and thus could spread yeast from patient to patient. However, Voss et al. investigated an apparent outbreak which occurred in our SICU in 1990 and demonstrated that the cluster was not caused by transmission of a single strain (34). Thus, we do not think that outbreaks explain the increased rates of nosocomial yeast infections in our hospital.

The importance of yeast infections at sites other than the bloodstream is not well defined. In addition, different investigators have used different definitions for fungal infections, especially for UTIs and gastrointestinal tract infections (20). However, using commonly accepted criteria for nosocomial UTIs, other investigators have shown that 25% of all UTIs in intensive care units were caused by *Candida* spp. (3, 18). Our results also document that fungal UTIs occur frequently and that the rate of these infections is increasing. In our institution, the rate of catheter-related UTIs in the SICU increased approximately fourfold over the study period, whereas the rate of surgical site yeast infections remained stable.

Several investigators have postulated that widespread use of fluconazole will select yeast species that are intrinsically resistant to this agent (28, 29, 37, 38). Some published reports appear to substantiate this hypothesis, but data from other reports have not (23, 36). At the University of Iowa Hospitals and Clinics, the incidence of infections caused by most non-*albicans Candida* species did not change substantially during the study period. However, the proportion of all nosocomial yeast infections caused by *C. glabrata* increased substantially and that of yeast infections caused by *C. albicans* decreased. These changes occurred coincident with increasing use of azoles (i.e., ketoconazole and fluconazole). However, the use of specific antifungal agents by different units and the yeast species causing nosocomial infections in those units did not appear to be related.

Other investigators have noted similar increases in the frequency of infections caused by *C. glabrata* in conjunction with azole use (1, 22, 24, 26). In a study by Nguyen et al., *C. glabrata* was the most common species other than *C. albicans* causing bloodstream infections (22). In addition, *C. glabrata* fungemia was associated with a high complication rate (e.g., endocarditis, osteomyelitis, hepatosplenic abscess) (22). Abi-Said et al. found that bloodstream infections caused by *C. glabrata* and *C. krusei* were more likely to occur in patients who had received fluconazole during hospitalization, whereas infections caused by *C. albicans* and *C. tropicalis* were more likely among patients who had not received that agent (1). In contrast, other investigators have noted that rates of infections caused by yeast species which are less susceptible to fluconazole, such as *C. krusei*, and *Saccharomyces* spp., usually increased before this drug was introduced or occurred as part of an outbreak (2, 5, 13, 17, 23, 39).

Except for FY 1990–1991, when *C. neoformans* caused 33% of the nosocomial yeast bloodstream infections, *C. albicans* was the predominant species causing nosocomial infections at this site. After fluconazole was introduced in our hospital, the proportion of bloodstream infections caused by *C. glabrata* increased but did not remain persistently elevated, as did the proportion of all yeast infections caused by this species. Thus, the incidence of *C. glabrata* bloodstream infections did not increase in parallel with the frequency of *C. glabrata* infections at other body sites.

In summary, we documented extensive use of fluconazole in our institution. Use of this agent varied among the different hospital units and was most intense in the BMTUs. In the gastrointestinal surgery unit, fluconazole was used most often

for empiric or prophylactic treatment. During the study period, rates of nosocomial yeast infection decreased precipitously in the adult BMTU. We do not know whether this change was caused by fluconazole use or by other factors not evaluated in this study. Conversely, despite increased use of fluconazole, rates of nosocomial yeast infection increased in the SICU and MICU. The proportion of infections caused by yeast species other than *C. albicans* did not increase consistently during the study period. However, *C. glabrata* became an important nosocomial pathogen during this period. Nationwide, *C. glabrata* is the second most common species of *Candida* causing nosocomial infections, and its presence is likely related to the selective pressure exerted by azoles.

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REFERENCES

1. **Abi-Said, D., E. Anaissie, O. Uzun, I. Raad, H. Pinzcowski, and S. Vartivarian.** 1997. The epidemiology of hematogenous candidiasis caused by different *Candida* species. Clin. Infect. Dis. **24:**1122–1128.
2. **Aucott, J. N., J. Fayen, H. Grossnicklas, A. Morrissey, M. M. Lederman, and R. A. Salata.** 1990. Invasive infection with *Saccharomyces cerevisiae*: report of three cases and review. Rev. Infect. Dis. **12:**406–411.
3. **Banerjee, S. N., T. G. Emori, D. H. Culver, R. P. Gaynes, W. R. Jarvis, T. Horan, J. R. Edwards, J. Tolson, T. Henderson, and W. J. Martone.** 1991. Secular trends in nosocomial primary bloodstream infections in the United States, 1980–1989. Am. J. Med. **91**(Suppl. 3B)**:**86S–89S.
4. **Beck-Sague, C. M., W. R. Jarvis, and The National Nosocomial Infections Surveillance System.** 1991. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980 to 1990. J. Infect. Dis. **167:**1247–1251.
5. **Berrouane, Y. F., R. J. Hollis, and M. A. Pfaller.** 1996. Strain variation among and antifungal susceptibilities of isolates of *Candida krusei*. J. Clin. Microbiol. **34:**1856–1858.
6. **Bodey, G. P.** 1992. Azole antifungal agents. Clin. Infect. Dis. **14**(Suppl. 1)**:**S161–S169.
7. **Borg-Von Zepelin, M., H. Eiffert, M. Kann, and R. Rüchel.** 1993. Changes in the spectrum of fungal isolates: results from clinical specimens gathered in 1987/88 compared with those in 1991/92 in the University Hospital Göttingen, Germany. Mycoses **36:**247–253.
8. **Broderick, A., M. Mori, M. D. Nettleman, S. A. Streed, and R. P. Wenzel.** 1990. Nosocomial infections: validation of surveillance and computer modeling to identify patients at risk. Am. J. Epidemiol. **131:**734–742.
9. **Bross, J., G. H. Talbot, G. Maislin, S. Hurwitz, and B. L. Strom.** 1989. Risk factors for nosocomial candidemia: a case-control study in adults without leukemia. Am. J. Med. **87:**614–620.
10. **Doebbeling, B. N., R. J. Hollis, H. D. Isenberg, R. P. Wenzel, and M. A. Pfaller.** 1991. Restriction fragment analysis of a *Candida tropicalis* outbreak of sternal wound infections. J. Clin. Microbiol. **29:**1268–1270.
11. **Fraser, V., M. Jones, J. Dunkel, S. Storfer, G. Medoff, and W. C. Dunagan.** 1992. Candidemia in a tertiary care hospital: epidemiology, risk factors, and predictors of mortality. Clin. Infect. Dis. **15:**414–421.
12. **Fridkin, S. K., and W. R. Jarvis.** 1996. Epidemiology of nosocomial fungal infections. Clin. Microbiol. Rev. **9:**499–511.
13. **Goldman, M., J. C. Pottage, and D. C. Weaver.** 1993. *Candida krusei* fungemia: report of 4 cases and review of the literature. Medicine (Baltimore) **72:**143–150.
14. **Goodman, J. L., D. J. Winston, R. A. Greenfield, P. H. Chandrasekar, B. Fox, H. Kaizer, R. K. Shadduck, T. C. Shea, P. Stiff, and D. J. Friedman.** 1992. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. N. Engl. J. Med. **326:**845–851.
15. **Grasela, T. H., S. D. Goodwin, M. T. Pasko, C. A. Walawander, and M. A. Raebel.** 1994. Use of antifungal therapy in hospitalized patients. I. Results prior to the marketing of fluconazole. Ann. Pharmacother. **28:**252–260.
16. **Grasela, T. H., M. T. Pasko, S. D. Goodwin, C. A. Walawander, N. Blackwelder, and R. J. Bruder-Holt.** 1994. Use of antifungal therapy in hospitalized patients. II. Results after the marketing of fluconazole. Ann. Pharmacother. **28:**261–270.
17. **Iwen, P. C., D. M. Kelly, E. C. Reed, and S. H. Hinrichs.** 1995. Invasive infection due to *Candida krusei* in immunocompromised patients not treated with fluconazole. Clin. Infect. Dis. **20:**342–347.
18. **Jarvis, W. R., J. R. Edwards, D. H. Culver, J. M. Hughes, T. Horan, T. G. Emori, S. Banerjee, J. Tolson, T. Henderson, and R. P. Gaynes.** 1991. Nosocomial infection rates in adults and pediatric intensive care units. Am. J. Med. **91:**185S–191S.
19. **Karabinis, A., C. Hill, B. Leclercq, C. Tancrede, D. Baume, and A. Andremont.** 1988. Risk factors for candidemia in cancer patients: a case-control study. J. Clin. Microbiol. **26:**429–432.
20. **Levine, J., R. K. Dykoski, and E. N. Janoff.** 1995. *Candida*-associated diarrhea: a syndrome in search of credibility. Clin. Infect. Dis. **21:**881–886.
21. **Meunier-Carpentier, F., T. E. Kiehn, and D. Armstrong.** 1981. Fungemia in the immunocompromised host: changing patterns, antigenemia, high mortality. Am. J. Med. **71:**363–370.
22. **Nguyen, M. H., J. E. Peacock, A. J. Morris, D. C. Tanner, M. L. Nguyen, D. R. Snydman, M. M. Wagener, M. G. Rinaldi, and V. L. Yu.** 1996. The changing face of candidemia: emergence of non-*Candida albicans* species and antifungal resistance. Am. J. Med. **100:**617–623.
23. **Pfaller, M. A.** 1996. Nosocomial candidiasis: emerging species, reservoirs, and modes of transmission. Clin. Infect. Dis. **22**(Suppl. 2)**:**S89–S94.
24. **Pfaller, M. A., R. N. Jones, S. A. Messer, M. B. Edmond, R. P. Wenzel, and The SCOPE Participant Group.** 1998. National surveillance of nosocomial blood stream infection due to species of *Candida* other than *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE program. Diagn. Microbiol. Infect. Dis. **30:**121–129.
25. **Pfaller, M. A., R. N. Jones, S. A. Messer, M. B. Edmond, and R. P. Wenzel.** 1997. National surveillance of nosocomial blood stream infection due to *Candida albicans*: frequency of occurrence and antifungal susceptibility in the SCOPE program. Diagn. Microbiol. Infect. Dis. **31:**327–332.
26. **Pfaller, M. A., S. A. Messer, A. Houston, M. S. Rangel-Frausto, T. Wiblin, H. M. Blumberg, J. E. Edwards, W. Jarvis, M. A. Martin, H. C. Neu, L. Saiman, J. E. Patterson, J. C. Dibb, C. M. Roldan, M. G. Rindaldi, and R. P. Wenzel.** 1998. National epidemiology of mycoses survey: a multicenter study of strain variation and antifungal susceptibility among isolates of *Candida* species. Diagn. Microbiol. Infect. Dis **31:**289–296.
27. **Powderly, W. G., D. M. Finkelstein, J. Feinberg, P. Frame, W. He, C. van der Horst, S. L. Koletar, M. E. Eyster, J. Carey, H. Waskin, T. M. Hooton, N. Hyslop, S. A. Spector, S. A. Bozzette, and The NIAID AIDS Clinical Trials Group.** 1995. A randomized trial comparing fluconazole with clotrimazole troches for the prevention of fungal infections in patients with advanced human immunodeficiency virus infection. N. Engl. J. Med. **332:**700–705.
28. **Price, M. F., M. T. LaRocco, and L. O. Gentry.** 1994. Fluconazole susceptibilities of *Candida* species and distribution of species recovered from blood cultures over a 5-year period. Antimicrob. Agents Chemother. **38:**1422–1424.
29. **Rex, J. H., M. G. Rinaldi, and M. A. Pfaller.** 1995. Resistance of *Candida* species to fluconazole. Antimicrob. Agents Chemother. **39:**1–8.
30. **Richardson, K., K. Cooper, M. S. Marriott, M. H. Tarbit, P. F. Troke, and P. J. Whittle.** 1990. Discovery of fluconazole, a novel antifungal agent. Rev. Infect. Dis. **12**(Suppl. 3)**:**S267–S271.
31. **Strausbaugh, L. J., D. L. Sewell, T. T. Ward, M. A. Pfaller, T. Heitzman, and R. Tjoelker.** 1994. High frequency of yeast carriage on hands of hospital personnel. J. Clin. Microbiol. **32:**2299–2300.
32. **U.S. Department of Health, Education, and Welfare.** 1972. Outline for surveillance and control of nosocomial infections. Centers for Disease Control, Atlanta, Ga.
33. **Vazquez, J. A., V. Sanchez, C. Dmuchowski, L. M. Dembry, J. D. Sobel, and M. J. Zervos.** 1993. Nosocomial acquisition of *Candida albicans*: an epidemiologic study. J. Infect. Dis. **168:**195–201.
34. **Voss, A., M. A. Pfaller, R. J. Hollis, J. Rhine-Calberg, and B. N. Doebbeling.** 1995. Investigation of *Candida albicans* transmission in a surgical intensive care unit cluster by using genomic DNA typing methods. J. Clin. Microbiol. **33:**576–580.
35. **Wey, S. B., M. Mori, M. A. Pfaller, R. F. Woolson, and R. P. Wenzel.** 1988. Hospital-acquired candidemia: the attributable mortality and excess length of stay. Arch. Intern. Med. **148:**2642–2645.
36. **Wingard, J. R.** 1995. Importance of *Candida* species other than *C. albicans* as pathogens in oncology patients. Clin. Infect. Dis. **20:**115–125.
37. **Wingard, J. R., W. G. Merz, M. G. Rinaldi, T. R. Johnson, J. E. Karp, and R. Saral.** 1991. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. N. Engl. J. Med. **325:**1274–1315.
38. **Wingard, J. R., W. G. Merz, M. G. Rinaldi, C. B. Miller, J. E. Karp, and R. Saral.** 1993. Association of *Torulopsis glabrata* infections with fluconazole prophylaxis in neutropenic bone marrow transplant patients. Antimicrob. Agents Chemother. **37:**1847–1849.
39. **Zerva, L., R. J. Hollis, and M. A. Pfaller.** 1996. In vitro susceptibility testing and DNA typing of *Saccharomyces cerevisiae* clinical isolates. J. Clin. Microbiol. **34:**3031–3034.